A. Regarding the Amendments

Claims 14 and 24 have been amended to remove the phrase "that selectively homes to brain." Attached herewith is an Appendix which shows the text deleted from claims 14 and 24 in bold and enclosed by brackets.

The amendment to claims 14 and 24 does not add new matter. Accordingly, Applicants respectfully request that the Examiner enter the claim amendment.

B. Regarding the rejection under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 14, 15, 17 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

The Examiner asserts that undue experimentation would have been required to practice the full scope of the claimed invention. Although the Examiner acknowledges that the specification provides enablement for the peptide consisting of the amino acid sequence CLSSRLDAC (SEQ ID NO:3), and also for this peptide fused to gene III, it is alleged that the specification lacks enablement for any peptide other than SEQ ID NO:3 or a gene III-peptide SEQ ID NO:3 fusion. The Examiner alleges that the skilled artisan would not have been able to

predict which peptides have activity without further experimentation.

Regarding gene III protein fusions and other peptide contexts

Applicants submit that the specification enables the full scope of the claims, including peptides in which a recited amino acid sequence, for example, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 or SEQ ID NO:16, is presented in a variety of contexts, including being fused to an amino acid sequence other than that of gene III. Applicants contend that there is no reason for the skilled artisan to conclude that activity of a peptide of the invention is dependent upon being presented as a gene III fusion.

In this regard, the specification teaches that activity of a peptide-gene III fusion is due to the library-encoded peptide sequence, rather than the gene III portion of the fusion. First, the specification discloses that free peptide SEQ ID NO:3 competes with the homing of phage displaying a SEQ ID NO:3-gene III fusion to brain (page 40, lines 20-27). These data demonstrate that peptide SEQ ID NO:3 maintains activity absent any additional peptide sequence. Further corroboration that the gene III portion of a peptide-gene III fusion is not required for activity is provided by data showing that administration of a SEQ ID NO:3/red blood cell conjugate to mice via the tail vein resulted in the presence of approximately twice as much of CLSSRLDAC (SEQ ID NO: 3)/RBC conjugate in harvested brain as in

kidney (page 34, lines 22-33). Thus, peptide SEQ ID NO: 3 maintained activity when fused to a moiety other than gene III.

Together, these data demonstrate both that peptide SEQ ID NO:3 has activity absent any additional sequence, and that peptide SEQ ID NO:3 has activity when fused to a moiety other than gene III. These data confirm, as would be expected by the skilled artisan, that there are no special properties associated with the gene III sequence that are required for activity of SEQ ID NO: 3 or another peptide of the invention.

Regarding establishing a Prima Facie case of non-enablement

Applicants are unaware of any special feature of the gene III sequence that would contribute to, or be required for, peptide activity. In this regard, Applicants respectfully remind the Examiner that it is not Applicants' burden to prove that the specification enables the invention; rather, the burden is on the Examiner to establish prima facie non-enablement. For the reasons set forth below, the Examiner has not met this burden.

As discussed above, the specification provides guidance to the skilled person to enable the claimed invention. The Examiner has provided no reasons for doubting this guidance and, furthermore, and has provided no credible specific technical reasons to support the purported lack of enablement, i.e., the assertion that only a gene III fusion protein, and not any other fusion protein, would have activity. As has been well-established by the courts, the Examiner must provide a

reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). For example, in regard to the Examiner's burden, the courts have indicated that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (*In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

While references are not absolutely required to support a *prima facie* case of lack of enablement, specific technical reasons are always required.

In the presence case, the only specific reasoning provided by the Examiner as a basis for the enablement rejection is a publication (Skolnick et al., Trends in Biotech. 18:34-39 (2000)), allegedly describing the unpredictable nature of peptide function. However, this reference provides no indication that a peptide having a specific amino acid sequence and contained in a gene III fusion would have altered activity when fused to a different sequence. Rather, the reference appears to describe difficulties associated with assigning protein function based on amino acid sequence or three-dimensional structure (see, for example, page 34, second column, fourth and fifth paragraphs, and

page 36, Figure 1 legend). The reference also describes difficulties associated with active site identification and identification of key residues required for a biochemical activity (page 35, first column).

The issues raised in Skolnick et al. would not appear applicable to the present invention. Firstly, any difficulties associated with assigning protein function are not relevant since the function of the peptides of the invention is not unknown; rather, these peptides are taught in the specification to home to brain (page 34, lines 3-24). Secondly, any difficulties associated with identification of key residues would not appear relevant since amino acid motifs or short amino acid sequences are taught in the specification (page 36, Table I). Provided with knowledge of both the amino acid motif or sequence and the activity of a peptide of the invention, one skilled in the art would not have been affected by the asserted difficulties set forth in Skolnick et al. Thus, the only specific evidence supplied by the Examiner in support of the enablement rejection is not relevant to the subject matter at hand.

In sum, the Examiner has not supplied any credible technical reasons in support of her assertion that the claimed peptides would not work in a variety of sequence contexts. Instead, the rejection is based on the assertion that the application does not disclose actual reduction to practice of peptides fused to sequences other than the gene III protein. Absent a reasonable basis for questioning enablement and specific

technical reasons, *prima facie* non-enablement has not been established.

Regarding homing to brain in preference to any other organ

The Examiner alleges that no exemplary peptide aside from peptide SEQ ID NO:3 was disclosed to home to any organ in comparison to any other organ.

Applicants submit that the claims do not include the limitation that a peptide home to brain in preference to any other organ. Firstly, claims 15 to 20 and 28 to 41 do not include a functional limitation. Thus, while the peptides of claims 15 to 20 and 28 to 41 are taught to be useful, for example, in targeting a moiety such as a drug to brain (page 5, lines 4-15), enablement of these peptides does not require that the peptides home to brain in preference to any other organ. This ground for rejection therefore is not relevant to claims 15 to 20 or 28 to 41.

Secondly, the remaining claims under examination (claims 14 and 24) also do not include the limitation that the peptides home to brain in preference to any other organ. Rather, claims 14 and 24, which are directed to X_1SRLX_2 (SEQ ID NO: 45) and X_3VLRX_4 (SEQ ID NO: 46) peptides, recite that the claimed peptides exhibit at least two-fold greater specific binding to brain than to kidney. In regard to the recited two-fold greater specific binding, Applicants note that all the peptides of the

invention were identified from multiple rounds of *in vivo* panning in which 6 or 13-fold more phage (CX_{5-7}/CX_9 library, second or third round, respectively), or 11 or 8-fold more phage ($X_2CX_{18}/X_2CX_{14}CX_2$, second or third round, respectively) bound to brain than to kidney (see page 33, line 20, to page 34, line 7). As further support for the recited at least two-fold greater specific binding, Applicants point out that the SRL-containing peptides SEQ ID NO: 1 and 3, which fall within claim 14, and the VLR-containing peptide SEQ ID NO: 16, which falls within claim 24, each were demonstrated to exhibit at least two-fold greater specific binding to brain than to kidney (8-fold, 8-fold and 9-fold, respectively)(see specification at page 37, lines 1-9). In sum, Applicants submit that the specification enables claims 14 and 24 as written.

In view of the above remarks, Applicants respectfully request that the Examiner remove this ground for rejecting the pending claims as allegedly lacking enablement.

Further regarding predictability

The Examiner states that the experimental procedures used in discovery of the peptides of the invention result in identification of peptide sequences which are unpredictable in nature other than by experimental isolation and testing.

Applicants submit that undue experimentation would not have been required to make and use the peptides of the invention.

In regard to claims 15 to 20 and 28 to 41, the specification teaches the structural features of the claimed peptides by providing the specific amino acid sequences of the peptides SEQ ID NOS:1, 5, 4, 16, 2, 6, 7, 8, and 9 (page 36, Table I). Regarding claims 14 and 24, directed to peptides SEQ ID NO:45 and SEQ ID NO:46, which contain SRL and VLR motifs, respectively, the specification teaches both the structural and functional characteristics of the claimed peptides. Specifically, the specification teaches the motif and number of flanking amino acids, as well as the recited functional characteristic that the peptide exhibits at least two-fold greater specific binding to brain than to kidney (see page 34, lines 13-18, page 36, Table I and page 37, lines 1-4).

Using routine methods of chemical synthesis, a skilled artisan would have been able to prepare a peptide of the invention without undue experimentation. Furthermore, in regard to the peptides of claims 14 and 24, one skilled in the art would have been able to confirm at least two-fold greater specific binding to brain than to kidney by, for example, tail vein injection into mice, following by harvesting of brain and kidney, as disclosed in Example II of the specification (see, for example, page 35, lines 3-15). Thus, only routine work would have been required for one skilled in the art to make a peptide having X_1SRLX_2 (SEQ ID NO: 45) and X_3VLRX_4 (SEQ ID NO: 46), and to corroborate that such a peptide exhibits two-fold greater specific binding to brain than to kidney, as recited in claims 14 and 24. Thus, using the guidance provided in the specification,

undue experimentation would not have been required to make or use any of the peptides of the invention.

Regarding "selective homing" in relation to claims 14 and 24

The claims also stand rejected as allegedly lacking enablement on the ground that the skilled artisan would have had reason to doubt that the peptide "selectively homed" to brain in the absence of data showing homing to brain in preference to any other control organ. Applicants note that, prior to the present amendment, only claims 14 and 24 recited the "selectively homes" language. Furthermore, although Applicants maintain that claims 14 and 24 are enabled as written, these claims have been amended to remove the phrase "that selectively homes to brain" in order to further prosecution. As written, claims 14 and 24 indicate that the claimed peptide "exhibits at least two-fold greater specific binding to brain than to kidney," and do not recite specific binding to brain in preference to any other organ. For these reasons, Applicants respectfully request that the Examiner remove this ground for rejection under the first paragraph of 35 U.S.C. § 112.

Having addressed each of the grounds for rejecting the claims as allegedly lacking enablement, Applicants submit that the full scope of the claims is enabled. Accordingly, Applicants respectfully request that the Examiner remove the rejection of claims 14 to 15, 17 to 20, 24 and 28 to 41 under 35 U.S.C. § 112, first paragraph.

C. Regarding the rejection under 35 U.S.C. § 103

The rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 103, as allegedly obvious over Smith and Scott, Meth. Enzymol. 217:228to257 (1993), and Koivunen et al. Cell Biol, 124:373to80 (1994), respectfully is traversed.

The Examiner indicates that the cited references describe production of phage display libraries in which randomly synthesized peptides are fused to the gene III protein using the fuse 5 vector. The Examiner observes that these libraries are taught in the specification as useful for *in vivo* panning, and asserts that the randomly synthesized peptides in the libraries of Smith and Scott and Koivunen et al. would have been expected to encompass the claimed peptides. The Examiner concludes that it would have been obvious to the skilled artisan to isolate from the phage vector a peptide encoded by the inserted randomly synthesized sequence.

Applicants submit that neither Smith et al. nor Koivunen et al. teach or suggest the claimed peptides, which are in isolated form. In particular, neither Smith et al. nor Koivunen et al. teach or suggest the specific recited amino acid motifs or sequences which are required structural features of the claimed isolated peptides. Specifically, neither Smith et al. nor Koivunen et al. teach or suggest the recited X_1SRLX_2 (SEQ ID NO: 45) motif, the recited X_3VLRX_4 (SEQ ID NO: 46) motif or any of the recited amino acid sequences (SEQ ID NOS: 1 to 9 and SEQ ID NO; 16). Rather than the claimed isolated peptides containing

one of the above amino acid motifs or sequences, the cited references merely report complex mixtures, or libraries, of phage displayed peptides containing, for example in a CX_7C library, approximately 20^7 phage-displayed peptides (see, for example, Koivunen et al., page 374, first column, third paragraph). Absent a teaching of the recited amino acid motifs and sequences, one skilled in the art would not have known which peptides to isolate from the libraries of the cited references and, therefore, would not have been able to make the peptides of the invention as they are claimed in isolated form. For this reason, the claimed isolated peptides are unobvious over the cited references by Smith and Scott and Koivunen et al.

Furthermore, Applicants submit that neither Smith and Scott nor Koivunen et al. is an enabling reference. Specifically, neither of the cited references teaches how to use the claimed isolated peptides. Without teaching how to use the invention, neither Smith and Scott nor Koivunen et al. meet the requirements of the first paragraph of 35 U.S.C. § 112 and, therefore, are not proper prior art. For this second reason, claims 14 to 20, 24 and 28 to 41 are unobvious over the cited references.

In view of the above remarks, Applicants respectfully request that the Examiner remove the rejection of claims 14 to 20, 24 and 28 to 41 under 35 U.S.C. § 103 as allegedly obvious over Smith and Scott and Koivunen et al.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

August 29, 2001
Date

Andrea L. Gashler

Andrea L. Gashler
Registration No.: 41,029
Telephone No. (858) 535-9001
Facsimile No. (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
7th Floor
San Diego, California 92122
USPTO CUSTOMER NO. 23601

Inventors: Ruoslahti and Pasqualini
Serial No.: 09/228,866
Filed: January 12, 1999

APPENDIX

The amendments to claims 14 and 24 in the present Response to Office Action is shown below. Text deleted from claims 14 and 24 is bolded and enclosed in brackets.

14. (Three times amended) An isolated peptide **[that selectively homes to brain]**, consisting of the amino acid sequence:

X_1SRLX_2 (SEQ ID NO: 45),

wherein X_1 and X_2 each is 1 to 10 independently selected amino acids

and wherein said peptide exhibits at least two-fold greater specific binding to brain than to kidney.

24. (Three times amended) An isolated peptide **[that selectively homes to brain]**, consisting of the amino acid sequence:

X_3VLRX_4 (SEQ ID NO: 46),

wherein X_3 is absent or is 1 to 10 independently selected amino acids and X_4 is 1 to 20 independently selected amino acids, and wherein said peptide is cyclic and exhibits at least two-fold greater specific binding to brain than to kidney.